DETAILED ACTION

Applicant's election with traverse of Group A, claims 1-10, 12, prostate cancer, in the reply filed on 09/05/08 is acknowledged.

The traversal is as follows:

The Examiner should not rely on an evaluation of novelty or unobviousness based on certain prior art in order to determine whether the requirement of unity of invention is satisfied under PCT Rule 13.1. Applicants should be given the opportunity to argue on merits during prosecution whether the claims are novel and unobvious over certain prior art. Restriction of the claims at this stage would deny Applicants such an opportunity.

Contrary to the Examiner's characterization, the present invention is not "inihibin", per se. Regarding WO98/47526, this document discloses that the onset of prostate cancer could be diagnosed by virtue of a decrease in the level of inhibin in a patient. The present application, however, is directed to the determination that in the context of an existing cancer, an increase in the level of inhibin is indicative of the shift of that cancer to an advanced/metastatic state.

Specifically, the claims of Groups A and B are both directed to detecting an increase in inhibin protein, with Group A relating to a determination of the onset of an advanced neoplasm, and Group B relating to a determination of predisposition to the onset of an advanced neoplasm. Similarly, the claims of Groups C and D are both directed to detecting an increase in inhibin nucleic acid, with Group C relating to a determination of the onset of an advanced neoplasm, and Group D relating to a determination of predisposition to the onset of an advanced neoplasm. All of Groups A-D are based on detecting an increase in the inhibin molecule. Therefore, Applicants

respectfully submit that Groups A-D are clearly linked to each other under a single inventive concept of detecting an increase in inhibin levels. Because WO'526 discloses absolutely nothing about an increase in inhibin levels in the context of any stage of any cancer, this technical feature of the present invention is a special technical feature and defines a contribution over the prior art. Therefore, the claims of Groups A-D should be examined together.

With respect to the election of neoplasm of prostate, diagnoses of different cancers are all based on the single inventive concept of detecting an increase in inhibin levels, and therefore methods in respect to different cancers should also be examined together.

This is not found persuasive because the claimed technical feature of the claimed invention is "inhibin" taught by WO98/47526, and the different methods of groups A-D, detecting different cancers or predisposition to different cancers, are different methods of use of "inhibin". If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).)

The requirement is still deemed proper and is therefore made FINAL.

In a telephonic conversation on 10/28/08 to the Attorney Xiaochun Zhu, Applicant was informed that claim 12 is withdrawn from consideration, as being drawn to non-elected invention.

Accordingly, Group A, claims 1-10, the level of inhibin protein, prostate cancer, are examined in the instant application.

The embodiment of claims 1-10, as drawn to: 1) a method for detecting the onset of an advanced neoplasm, by detecting the level of inhibin nucleic acid, 2) a method detecting predisposition to developing an advanced neoplasm, or 3) a method for detecting the onset of an advanced neoplasm other than prostate cancer, has been withdrawn from consideration as being drawn to non-elected invention.

Objection

The specification is objected to, because the published date of the cited reference of Robertson et al, on page 28, last line, bridging page 29 of the instant application, is missing.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1-10 are indefinite for the use of the relative term "advanced" neoplasm in claims 1-2, 4-5. "Advanced" neoplasm does not necessarily mean an increased prostate cancer stage, because when compared to non-cancerous prostate, any stage of prostate cancer would be advanced neoplasm.

2. Claims 1, 3-10 are indefinite, because it is not clear in claim 1 an "increase" in the level of inhibin is as compared to what.

3. Claim 7 is indefinite for the use of the language "amino acids 73-96 of the alpha-C region", without a sequence identification number for the alpha-C region, because there is no point of reference for amino acids 73-96, in view that alpha-inhibin may have different forms, as suggested in the specification (p.28, last paragraph), and the sizes and structure of their amino acid sequences are not known.

Claim Rejections - 35 USC § 112, First Paragraph, Deposit Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses that the monoclonal antibody PO#12 binding to amino acids 73-96 of the alpha-C region of inhibin, is as published in Robertson et al, 2001, Mol Cell Endo, 180: 79-86 (p.28, last line, bridging p.29). There is however no information concerning the deposition of the monoclonal antibody PO#12. Further, it is not clear whether all restrictions upon public access to the deposits will be irrevocably removed upon the granting of a patent on this application, and that the deposit will be replaced if viable samples cannot be dispensed by the depository.

Claim 9 is rejected under the deposit rule requirement, because one cannot predict the characteristics required by the monoclonal antibody PO#12 without its public availability. A deposit for patent purposes of the monoclonal antibody PO#12 or the hybridoma cell lines producing the monoclonal antibody PO#12 is required to enable the invention of claim 9, because it is not clear that the monoclonal antibody PO#12 or the cell lines possessing the identical structure and functional properties of those producing the monoclonal antibody PO#12 are known and publicly available or can be reproducibly isolated without undue experimentation. Without a publicly available deposit of the monoclonal antibody PO#12 or the cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the monoclonal antibody PO#12, or the cell lines which produce chemically and functionally distinct antibodies is an unpredictable event. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequence to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementary determining regions, can be folded to form similar binding contours, which result in similar immunochemical characteristics (William E. Paul, ed., 3rd ed. 1993, Fundamental Immunology, p. 242).

Further, Applicant is required to submit a statement, reciting that all restrictions upon public access to the deposits will be irrevocably removed upon the granting of a patent on this application, and that the deposit will be replaced if viable samples cannot be dispensed by the depository. See CFR 1.801-CFR 1.809.

In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification discloses that the level of alpha-inhibin protein in prostate cancer tissue is increased in Gleason grade 4 as compared to that in Gleason grade 3 prostate cancer, using monoclonal antibody PO#12, which binds to amino acids 73-96 of the alpha-C region of inhibin. (Example 4 on page 74). The specification discloses that however an antibody to the N-terminal amino acids 3-24 of the alpha C- region subunit of inhibin does not detect the presence of the

form of alpha-inhibin which is increased in prostate biopsy samples exhibiting the onset of advanced cancer (p. 28, last paragraph bridging p.29). The specification suggests that alpha-inhibin may undergo different forms and/or cleavage at the alpha C-region of the alpha-inhibin subunit (p.28, last paragraph). It is **not clear however the exact amino acids** of the presumed detected form of the alpha-C region of inhibin comprising amino acids 73-96 of the alpha-C region. The specification also discloses that for prostate cancers, excluding those having 100% Gleason grade 3, the level of alpha-inhibin is increased as compared to non-tumor tissues, or benign prostate glands, using monoclonal antibody PO #12 (p.70, first paragraph, and Example 2 on pages 70-71). The specification discloses that patients having 100% Gleason grade 3 are excluded because they have no incidence of recurrent disease in >=5 years (p.66, first paragraph). The specification discloses that the percent of Gleason grade 4/5 is 44.1% in a total sample of 107 patients (Table 2 on page 77). It is not clear in the specification, what other Gleason grades above grade 4/5 are included in the samples.

1. The claims encompass **a method for detecting an advanced prostate cancer**, comprising detecting an increase or modulation in the level of full length inhibin protein, full length alpha-inhibin, or full length alpha-C region.

The encompassed modulation in the level of inhibin protein, as claimed in claim 2, is interpreted as an increase of said level in this enablement rejection. Further, due to the open language "comprises" in claim 8, the encompassed detected sequence in claim 8 is the alpha-C region.

Since it is not clear that in claim 1, the increase level is compared to what, and in claim 2, what constitutes a "normal level", one would not know how to perform the claimed method.

Similarly, since there is no point of reference for amino acids 73-96 of the alpha-C region of inhibin, one would not know how to make the claimed detected antigen as claimed in claim 8.

Further, one cannot predict that an **increase** in the level of inhibin, alpha-inhibin, or alpha C-region of inhibin would be detected in prostate cancer having Gleason grade 4 and 5, which is encompassed as advanced prostate cancer in the claimed method, in view of the following contradictory teaching in the art. Mellor et al, 1998, J Clin Endocrinol Metab, 83: 969-975, IDS of 09/13/07, teach that in men with high grade carcinoma of prostate cancer, having Gleason grade 4 and 5, the level of alpha-inhibin, as detected by antibodies to the **C or N terminal** regions of the alpha-inhibin, is **decreased** as compared to adjacent non-malignant prostate tissue, or prostate tissue of benign prostate patients (BPH) (p.969, second column, last paragraph, bridging p.970). Antibodies to the C or N terminal regions of the alpha-inhibin would detect inhibin, alpha-inhibin, or alpha C-region of inhibin, which region would comprise amino acids 73-96.

2. Moreover, **progression of an advanced prostate cancer**, as claimed in claims 2-10, encompasses progression, for example, from Gleason grade 4/5 to higher Gleason grades, such as Gleason grades 6-10. One cannot predict that there is a modulation, or increase of inhibin, alpha-inhibin, or alpha-C-region level in such progression, because the level of inhibin protein in different Gleason grade prostate cancer is not predictable.

3. In addition, although the level of a specific form of alpha-C region inhibin detected by monoclonal antiboby PO#12 increases in prostate cancer having Gleason score grade 4/5, as compared to prostate cancer having Gleason score grade 3, one cannot predict that the level of said form is increased in **any biological sample, such as serum, bodily fluid,**

extracellular medium, or supernatants, or cell culture medium, and is the same as that in prostate cancer tissue, because there is no indication that said specific form of inhibin is a secreted protein. Further, even if said form of inhibin were a secreted protein, one cannot predict that the level of said specific form of inhibin in any biological sample, such as serum, bodily fluid, extracellular medium, or supernatants is the same as that in prostate cancer tissue, due to for example, difference in rate of clearance of inhibin. In addition, one cannot predict that in vitro cell culture, or its culture medium would have the same level of inhibin as prostate cancer tissue, due to the well known cell culture artifact. Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Embleton et al, 1984 (Immunol Ser, 23:181-207) teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Tian, J et al, 2004 (Physiol Genomics, 17: 170-182), teach culture-induced artifact in macular RPE cells, wherein 950 genes are differentially expressed between native RPE and cultured RPE cells, and wherein 2080 genes are expressed in cultured RPE cells but are not expressed in native RPE cells (abstract, p.176). Kunkel, P, et al, 2001 (Neuro-oncology 3(2): 82-88), teach that teach that scatter factor/hepatocyte growth factor is overexpressed in most tumors examined, including glioblastomas, and that the lack of expression of scatter factor/hepatocyte growth factor in most cultured glioblastoma cells is not representative of the in vivo situation, and most likely represents a culture artifact (abstract). The evidence presented thus clearly demonstrates that in

cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays For the reasons set forth above, one cannot predict that in vitro cell culture would have the same level of the specific form of alpha-C region of inhibin detected by monoclonal antibody PO#12 as in prostate cancer tissue.

4. Further, since **neoplasm,** as claimed in claims 1-3, 5-10, encompasses any abnormal growth, which is not necessarily cancerous (Stedman's medical dictionary, 25th ed, 1990, p. 1029-1030), one cannot predict a successful detection of the onset or progression of advanced prostate cancer, wherein the cells to be assessed are neoplastic cells, which are not necessarily cancerous, and are unrelated to cancer, and thus having different etiology and characteristics, and would not predictably have the same level of inhibin protein.

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-8, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Garde et al, 1994, Cancer Letters, 78: 11-17.

Claims 1-8, 10 are as follows:

1. (Original) A method of detecting the onset of an advanced neoplasm in a mammal said method comprising screening for the level of inhibin protein and/or gene expression in a biological sample derived from said mammal wherein an increase in the level of inhibin and/or gene expression is indicative of the onset of an advanced neoplasm.

2. (Original) A method of monitoring for the onset or progression of an advanced neoplasm in a mammal said method comprising screening for the modulation in the level of inhibin in a biological sample derived from said mammal wherein the level of said inhibin relative to the normal level of inhibin is indicative of the onset or progression of an advanced neoplasm.

3. (Original) The method according to claim 1 or 2 wherein the biological sample is selected from the group including serum, tissue extract, body fluids, cell culture medium, extracellular medium, supernatants, biopsy specimens or resected tissue.

4. (Currently Amended) The method according to claim 3 wherein said advanced neoplasm is an advanced malignant neoplasm.

5. (Original) The method according to claim 4 wherein said advanced malignant neoplasm is a metastatic neoplasm.

6. (Currently Amended) The method according to claim 1 or 2 wherein said inhibin is alpha-inhibin.

7. (Original) The method according to claim 6 wherein said a-inhibin is the alpha C region of the alpha-inhibin protein.

8. (Original) The method according to claim 7 wherein said alpha-C region comprises amino acids 73-96 of the alpha-C region.

10. (Currently Amended) The method according to claim 1 or 2 wherein said neoplasm is a neoplasm of the prostate.

The language "is" in "inhibin is alpha-inhibin protein", and "alpha-inhibin is the alpha C region of the alpha-inhibin protein" as claimed in claims 6 and 7, respectively, is interpreted as open language, and has the same meaning as "comprises". "Wherein an increase in the level of inhibin and/or gene expression is indicative of the onset of an advanced neoplasm" as claimed in claim 1, and "wherein the level of said inhibin relative to the normal level of inhibin is indicative of the onset or progression of an advanced neoplasm" as claimed in claim 2 are reasonably

interpreted as a mental process, and not a method step. Further, modulation as claimed in claim 2 is interpreted as a decrease or an increase in this rejection.

Garde et al teach that the prostate inhibin peptide is a marker of prostate cancer, and that a strong staining of prostate inhibin peptide is found in metastatic prostate cancer sample, and negative staining in all cases of non-prostatic carcinoma (abstract, p.14, second column).

Although the reference does not explicitly teach that inhibin is alpha-inhibin protein, or the alpha C region of the alpha-inhibin protein, wherein said alpha-C region comprises amino acids 73-96 of the alpha-C region, however, the claimed inhibin protein appears to be the same as the prior art inhibin protein. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

2. Claims 2-4, 6-8, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Mellor et al, 1998, J Clin Endocrinol Metab, 83: 969-975, IDS of 09/13/07.

Claims 2-4, 6-8, 10 are as follows:

2. (Original) A method of monitoring for the onset or progression of an advanced neoplasm in a mammal said method comprising screening for the modulation in the level of inhibin in a biological sample derived from said mammal wherein the level of said inhibin relative to the normal level of inhibin is indicative of the onset or progression of an advanced neoplasm.

3. (Original) The method according to claim 1 or 2 wherein the biological sample is selected from the group including serum, tissue extract, body fluids, cell culture medium, extracellular medium, supernatants, biopsy specimens or resected tissue.

4. (Currently Amended) The method according to claim 3 wherein said advanced neoplasm is an advanced malignant neoplasm.

6. (Currently Amended) The method according to claim 1 or 2 wherein said inhibin is alpha-inhibin.

7. (Original) The method according to claim 6 wherein said a-inhibin is the aC region of the alpha-inhibin protein.

8. (Original) The method according to claim 7 wherein said alpha-C region comprises amino acids 73-96 of the alpha-C region.

10. (Currently Amended) The method according to claim 1 or 2 wherein said neoplasm is a neoplasm of the prostate.

Modulation as claimed in claim 2 is interpreted as a decrease or an increase in this rejection.

Mellor et al teach detection of a decrease in the level of alpha-inhibin in prostate cancer tissue with high grade carcinoma, having Gleason grade 4 and 5, using antibodies to the C or N

terminal region of the alpha-inhibin subunit, as compared to adjacent non-malignant prostate tissue, or prostate tissue of benign prostate patients (BPH) (p.969, second column, last paragraph, bridging p.970).

Although the reference does not explicitly teach that inhibin alpha-C region comprises amino acids 73-96 of the alpha-C region, however, the claimed inhibin appears to be the same as the prior art inhibin. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH-TAM DAVIS
October 28, 2008

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643